REMARKS

Rejection under §101 and §112, paragraph

It is stated on Page 3 of the Office action dated October 21, 2004: "The specification has not provided one of skill in the art with any evidence that the up-regulation of the mRNA is in any way correlative to the up-regulation of the protein itself, nor provided any information on the protein, or whether the protein is translated at up-regulated levels. Thus the intended utility of the protein as a marker for angiogenesis or vasculogenesis has not been clearly set forth in the specification so that one of skill reading the disclosure of the instant invention is able to clearly determine that the utility is evident" See, also Page 4 of the Office action.

Applicant respectfully traverses this rejection. According to M.P.E.P. §2107.02: "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." The examiner has not provided any basis to doubt the assertions in the specification that ANH401 polypeptide could be used a marker for angiogenesis. See, e.g., Specification, beginning on Page 34, line 10.

To the contrary, it is stated on Page 468 of the attachment (Exhibit 1) from the *Molecular Biology of the Cell*, that "transcription (transcriptional control) usually predominates" in "the pathway from RNA to protein." This would have led to the reasonable expectation that expression of RNA would result in the production of the protein it encodes, and that increased RNA levels would be correspondingly associated with increased protein levels. Thus, the skilled worker would have had no reasonable basis to doubt the statements in the specification.

Moreover, the protein, itself, could be used as marker for expression of the nucleic acid coding for it, providing an additional and well-known utility for it. The declaration provided by

Dr. Zairen Sun clearly establishes up-regulation of its mRNA, a fact conceded by the examiner. (Office action, Page 3: "The specification has only provided evidence of the mRNA coding the protein of the instant invention in tissues associated with angiogenesis", Page 4: "The declaration demonstrates that the mRNA term ANH401 is expressed at relatively low levels at times of non angiogeneic [sic] activity and is highly expressed during times of angiogenesis."). Thus, if the nucleic acid were transfected and expressed in, e.g., insect cells, appearance of the protein could be used to determine those cells which successfully expressed it, analogously to how selectable markers are utilized. In this case, utility is attributed to the nucleic acid as a marker for angiogenesis, and the utility of the protein it encodes is to detect its production in transfected cells. The expression of the nucleic acid in cell lines would be useful, e.g., for making large quantities of it to use as hybridization probe. The fact that the nucleic acid is useful confers utility on its many facets, including the protein it encodes.

Contrary to the examiner's analysis on Page 3 of the Office action, Example 12 of the Utility Guidelines is relevant to the utility issue. The examiner states that that "the protein [of Example 12] has already been established as having an activity and has actually been shown to be differentially expressed in some tissue." In fact, the biological function of the receptor was not identified in the hypothetical posed by the Patent Office, and its ability to bind to protein X, alone, was rejected as adequate to satisfy the statutory utility requirements.. See, *Utility Guidelines*, Page 66. The analysis changed *only* when the hypothetical specification was modified to disclose differential expression in cancer cells.

The claims have been amended by the addition of hybridization language. This format was stated by the Patent Office to conform to the requirements of §112, first paragraph. The recited hybridization conditions yield structurally similar sequences. See, *Synopsis of Written Description Guidelines*, Example 9; *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). It is believed that this addresses the rejection of Claim 8 on Pages 6-9 of the Office action.

Rejection under §112, first paragraph (Office action, Page 5)

The amendment to Claim 8 is supported by the specification as originally filed. Page 4, lines 16-17 refer to amino acids 303-308 in Fig. 1 which corresponds to the amino acids recited in the claim. Moreover, even if this explicit disclosure were not present in the specification, the amendment would have support in Fig.1 which shows the recited sequence as an insertion in AF326966. It is entirely appropriate to rely on drawings for written description purposes. See, *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

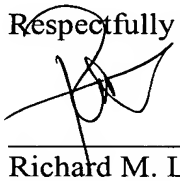

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EXHIBIT

1

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Front cover: The photograph shows a rat nerve cell in culture. It is labeled (*yellow*) with a fluorescent antibody that stains its cell body and dendritic processes. Nerve terminals (*green*) from other neurons (not visible), which have made synapses on the cell, are labeled with a different antibody. (Courtesy of Olaf Mundigl and Pietro de Camilli.)

Dedication page: Gavin Borden, late president of Garland Publishing, weathered in during his mid-1980s climb near Mount McKinley with MBoC author Bruce Alberts and famous mountaineer guide Mugs Stump (1940–1992).

Back cover: The authors, in alphabetical order, crossing Abbey Road in London on their way to lunch. Much of this third edition was written in a house just around the corner. (Photograph by Richard Olivier.)

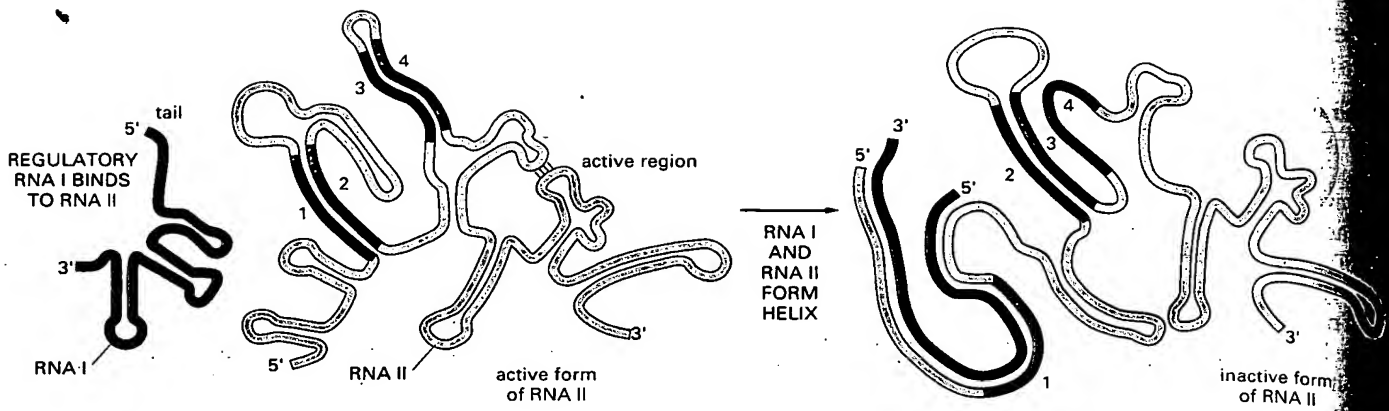

Figure 9–89 Antisense RNA strategy for regulating plasmid numbers in bacteria. A regulatory interaction between two RNA molecules maintains a constant plasmid copy number in the ColE1 family of bacterial DNA plasmids. RNA I (about 100 nucleotides long) is a regulatory RNA that inhibits the activity of RNA II (about 500 nucleotides long), which normally helps initiate plasmid DNA replication. The concentration of RNA I increases in proportion to the number of plasmid DNA molecules in the cell, so that as plasmid numbers increase, plasmid replication is inhibited. RNA I is complementary in sequence to the 5′ end of RNA II. In RNA II sequence 2 is complementary to both sequence 1 and sequence 3, and it is displaced from one to the other by the binding of RNA I; RNA I thereby alters the conformation of sequence 4, inactivating RNA II. (After H. Masukata and J. Tomizawa, *Cell* 44:125–136, 1986.)

accomplished by specialized RNA-binding proteins. In other cases, however, the recognition of specific RNA sequences is carried out by other RNA molecules, which use complementary RNA-RNA base-pairing as part of their recognition mechanism. RNA-RNA pairings, for example, are known to play a central part in translation, in RNA splicing, in several other forms of RNA processing, and in the RNA editing that occurs in trypanosomes. In attempting to dissect posttranscriptional mechanisms, we have largely entered an RNA world.

RNA molecules also have other regulatory roles in cells. The *antisense RNA* strategy for experimentally manipulating cells so that they fail to express a particular gene (see p. 326) mimics a normal mechanism that is known to regulate the expression of a few selected genes in bacteria and may be used much more widely than is now realized. A well-understood example of this kind of mechanism provides a feedback control on the initiation of DNA replication for a large family of bacterial DNA plasmids. The control system limits the number of copies of the plasmid made in the cell, thereby preventing the plasmid from killing its host cell by overreplicating (Figure 9–89).

Studies of RNA-catalyzed reactions are of special interest from an evolutionary perspective. As discussed in Chapter 1, the first cells are thought to have lacked DNA and may have contained very few, if any, proteins. Many of the RNA-catalyzed reactions in present-day cells seem to represent molecular fossils—descendants of the complex network of RNA-mediated reactions that are presumed to have dominated cell metabolism more than 3.5 billion years ago. Recombinant DNA technology has allowed large amounts of pure RNAs of any sequence to be produced *in vitro* with purified RNA polymerases (see Figure 7–36), making it possible to study the detailed chemistry of RNA-catalyzed reactions. From an understanding of many such reactions, biologists hope to be able to trace the path by which a living cell first evolved.

Summary

Many steps in the pathway from RNA to protein are regulated by cells to control gene expression. Most genes are thought to be regulated at multiple levels, although control of the initiation of transcription (transcriptional control) usually predominates. Some genes, however, are transcribed at a constant level and turned on and off solely by posttranscriptional regulatory processes. These processes include (1) attenuation of the RNA transcript by its premature termination, (2) alternative RNA splice-site selection, (3) control of 3′-end formation by cleavage and poly-A addition, (4) control of transport from the nucleus to the cytosol, (5) localization of mRNAs to particular parts of the cell, (6) RNA editing, (7) control of translational initiation, (8) regulated mRNA degradation, and (9) translational recoding. Most of these control processes require the recognition of specific sequences or structures in the RNA molecule being regulated. This recognition can be accomplished by either a regulatory protein or a regulatory RNA molecule.